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A multicentre randomised controlled study to evaluate whether Neuromuscular Electrical Stimulation improves the absolute walking distance in patients with Intermittent Claudication compared to best available treatment. (NESIC) [ISRCTN 18242823]

Authors:

Rebecca Lawton<sup>1</sup>, Adarsh Babber<sup>1</sup>, Bruce Braithwaite<sup>2</sup>, Laura Burgess<sup>3</sup>, Laura J Burgess<sup>1</sup>, Ian Chetter<sup>4</sup>, James Coulston<sup>5</sup>, David Epstein<sup>6</sup>, Francesca Fiorentino<sup>7</sup>, Manjit Gohel<sup>8</sup>, Francine Heatley<sup>1</sup>, Robert Hinchliffe<sup>9</sup>, Sarah Horgan<sup>10</sup>, Nandita Pal<sup>11</sup>, Joseph Shalhoub<sup>1</sup>, Richard Simpson<sup>2</sup>, Gerard Stansby<sup>12</sup> Alun H Davies<sup>1,2</sup>

<sup>1</sup>Academic Section of Vascular Surgery, Department of Surgery & Cancer, Imperial College London

Email: [r.lawton@imperial.ac.uk](mailto:r.lawton@imperial.ac.uk); [a.babber@imperial.ac.uk](mailto:a.babber@imperial.ac.uk); [l.burgess@imperial.ac.uk](mailto:l.burgess@imperial.ac.uk); [f.heatley@imperial.ac.uk](mailto:f.heatley@imperial.ac.uk); [j.shalhoub@imperial.ac.uk](mailto:j.shalhoub@imperial.ac.uk); [a.h.davies@imperial.ac.uk](mailto:a.h.davies@imperial.ac.uk)

<sup>2</sup>Nottingham University Hospitals NHS Trust, UK

Email: [bruce.braithwaite@nhs.net](mailto:bruce.braithwaite@nhs.net); [Richard.Simpson@nuh.nhs.uk](mailto:Richard.Simpson@nuh.nhs.uk)

<sup>3</sup>Imperial College Healthcare NHS Trust, UK

Email: [laura.burgess7@nhs.net](mailto:laura.burgess7@nhs.net); [a.h.davies@imperial.ac.uk](mailto:a.h.davies@imperial.ac.uk)

<sup>4</sup>Hull Royal Infirmary, UK

Email: [ian.chetter@hey.nhs.uk](mailto:ian.chetter@hey.nhs.uk)

<sup>5</sup>Taunton and Somerset NHS Foundation Trust, UK

Email: [james.coulston@tst.nhs.uk](mailto:james.coulston@tst.nhs.uk)

<sup>6</sup>University of Granada, UK

Email: [david.epstein@york.ac.uk](mailto:david.epstein@york.ac.uk)

<sup>7</sup>Imperial Clinical Trials Unit Imperial College London, UK

Email: [f.florentino@imperial.ac.uk](mailto:f.florentino@imperial.ac.uk)

<sup>8</sup>Cambridge University Hospitals NHS Foundation Trust, UK

Email: [manjit.gohel@addenbrookes.nhs.uk](mailto:manjit.gohel@addenbrookes.nhs.uk)

<sup>9</sup>North Bristol NHS Trust, UK

Email: [robert.hinchliffe@bristol.ac.uk](mailto:robert.hinchliffe@bristol.ac.uk)

<sup>10</sup>Lay patient representative, UK

Email: [sarahhorgan@btinternet.com](mailto:sarahhorgan@btinternet.com)

<sup>11</sup>University Hospital Southampton NHS Foundation Trust, UK

Email: [nanditapal@doctors.org.uk](mailto:nanditapal@doctors.org.uk)

<sup>12</sup> Northern Vascular Unit, University of Newcastle upon Tyne, UK

Email: [Gerard.Stansby@nuth.nhs.uk](mailto:Gerard.Stansby@nuth.nhs.uk)

## **For Correspondence**

Alun H Davies

Professor of Vascular Surgery

Head, Academic Section of Vascular Surgery

Department of Surgery & Cancer

Imperial College London

4<sup>th</sup> Floor, East Wing, Charing Cross Hospital

Fulham Palace Road

London, W6 8RF, UK

E mail:      [a.h.davies@imperial.ac.uk](mailto:a.h.davies@imperial.ac.uk)

Tel:            +44 (0) 20 3311 7320

Fax:            +44 (0) 20 3311 7362

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Abstract:

*Objective:*

To assess the clinical efficacy of an NMES device to improve the absolute walking distance (AWD) in patients with IC, as an adjunct to the local standard care available at the study sites compared to local standard care alone.

*Methods:*

An open, multicentre, randomised controlled trial including eight participating centres in England. Sites are equally distributed between those that provide SET programmes and those that do not. Patients with IC meeting the inclusion and exclusion criteria, and providing consent will be randomised, depending on the centre type, to either NMES and locally available standard care or standard care alone. The primary endpoint, AWD, will be measured at 3 months (the end of the intervention period) by treadmill testing. Secondary outcomes include quality of life assessment, compliance with the interventions, economic evaluation of the NMES device, and lower limb haemodynamic measures to further the understanding of underlying mechanisms. Recruitment is due to commence in February 2018 and will continue for a total of 15 months. The NESIC trial is funded by the UK Efficacy and Mechanism Evaluation (EME) Programme, Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. ISRCTN 18242823.

**Keywords**

Randomised controlled trial, supervised exercise therapy, neuromuscular electrical stimulation, intermittent claudication, absolute walking distance.

## **Introduction**

Intermittent claudication (IC) describes pain in the lower limbs brought on by exertion and relieved by rest. It is the commonest manifestation of peripheral arterial disease (PAD) and has a significant impact on patients' exercise tolerance and quality of life (QoL). In the UK, approximately 5-10% of adults aged over 55 years are estimated to be suffering with IC (1). With an ageing population, the prevalence of IC and its associated health burdens are expected to grow (2).

Under the remit of the UK National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme, the study investigators have designed a randomised controlled trial to determine definitive clinical efficacy, mechanistic evaluation and cost effectiveness of a novel intervention that has the potential to significantly impact care provision and outcomes for patients with IC. In an increasingly stretched healthcare system, with barriers to both supervised exercise therapy (SET) provision and attendance, the addition of a more accessible, safe and effective non-invasive modality, will provide greater flexibility for clinicians and patients in the first-line management of IC and its associated health burdens.

## **Supervised exercise therapy**

UK clinical guidelines published in 2012 by the National Institute for Health and Care Excellence (NICE) recommend that all patients diagnosed with IC are offered a programme of SET in addition to best medical therapy (BMT), which includes exercise advice (3). The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force on Practice Guidelines (4), Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) (5) and European Society of

Cardiology(ESC) guidelines in collaboration with The European Society for Vascular Surgery (ESVS) (6) all support a Level 1 recommendation for supervised exercise therapy in the treatment of claudication.

Studies have shown SET to significantly improve walking distance with a sustained effect over time. A Cochrane systematic review of the impact of SET on walking distances was carried out in 2006 by Bendermacher et al (7), and was repeated with updated study data in 2013 by Fokkenrood et al (8). The latter review included randomised controlled trial data comparing SET to non-SET management in patients with IC. Fourteen studies were included, randomising a total of 1002 participants, followed up for a duration of between 6 weeks and 12 months. The primary outcome was absolute walking distance (AWD) as measured by treadmill testing. There was a significant improvement of AWD with an effect size of 0.69 (95% Confidence Interval (CI) 0.51-0.86) and 0.48 (95% CI 0.32-0.64) at 3 months and 6 months, respectively. On average, there was an improvement in AWD of approximately 180 metres in the SET group (8).

SET programmes involve at least 30 minutes of physical activity, including various low impact exercises, specifically designed to target the lower limbs. Although the duration of programmes can vary across UK healthcare trusts, SET is usually carried out within a secondary care setting and is supervised by a healthcare practitioner (physiotherapist or nurse specialist) once a week for a 3-month period. The SET programme for NESIC will be administered as per local guidelines and is not standardised by this protocol, although all are based upon NICE Clinical Guideline 147 (3).

BMT is designed to address cardiovascular risk factors, including smoking cessation, statins and antiplatelet use, diet and weight management, prevention, diagnosis and management of

diabetes, high blood pressure, and other cardiovascular risk factors. It is delivered alongside local standard care, verbal exercise advice and/or referral for SET.

### **Availability of supervised exercise therapy**

Although SET for patients with IC remains the standard of care, access to programmes varies significantly amongst secondary care providers across the UK. A postal survey audit published by Shalhoub et al in 2009 (9) showed that only 24% of 84 responding UK vascular surgeons had access to SET for their IC patients. An online survey audit repeated in 2014 by Babber et al (10) was the first audit of SET access following the publication of the 2012 NICE guidance and was open to vascular surgeons in the UK and Ireland, as well as to members of a physiotherapy organisation as the main SET providers. This audit showed only 35% of 118 respondents had access to SET.

A study in 2017 by Harwood et al (11) investigated why access to SET may be poor, citing funding as the most common barrier to initiating SET programmes in secondary care (33/35; 94.3%). Other reasons including the lack of appropriate staff, facilities and expertise were also cited across 49 NHS Trusts (12).

Where SET was available, patient compliance was a major concern due to difficulties travelling to the SET class, travel expenditure and time away from work preventing attendance. Further studies have also cited patient resistance as well as professional self-interest as preventing the widespread uptake of SET classes across the UK (13).

In the US there is a well-established evidence base supporting the use of supervised exercise in patients with PAD. However, reimbursement via insurance has been limited and SET has been underutilised as a result (14). This may change following a 2017 Decision Memo from The Centers for Medicare and Medicaid Services (CMS), which announced that the evidence



is sufficient for patients with PAD to receive SET through Medicare. Both patient and clinician uptake, and longer term success of such programmes is as yet unknown (15).

In summary, despite clear evidence that SET has significant clinical benefit in patients with IC, both clinicians and patients seem unable to fully utilise this non-invasive treatment modality as part of first line therapy.

### **Neuromuscular electrical stimulation as an adjunct to supervised exercise therapy**

Neuromuscular electrical stimulation (NMES) is a non-invasive, low cost treatment strategy for patients with IC. The application of NMES has been utilised to enhance peripheral circulation. However, as an emerging technology in venous disorders, it has not been properly assessed for efficacy in a fully powered clinical trial.

A pilot study by Varatharajan et al, showed improvements in arterial and venous blood flow and time averaged mean velocity during the use of an NMES device, which returned to baseline once stimulation stopped (16). A subsequent proof of concept pilot study of 20 patients with IC showed a significant improvement in AWD (102.3m vs.187.2m,  $p<0.01$ ), and both 'disease specific' and 'generic' health related QoL measures after using a commercially available NMES device for 6 weeks (12). Compliance as assessed by patient recorded diaries was 98.5% in the 6-week follow-up period. A systematic review by Williams et al included 5 studies utilising various NMES devices as treatment for patients with IC (17). Ninety-six patients with IC were compared between control and NMES groups in the 5 included studies and identified up to 150% improvement in AWD at 4 weeks of intervention and 34% at 8 weeks.

In the NESIC protocol, patients will be supplied with the Revitive IX, a CE marked class IIa device designed to provide a pre-programmed session of electrical stimulation to the plantar

aspect of the feet whilst the user is seated. The user controls the intensity of the impulses, and therapeutic benefit is deemed to occur when impulses are sufficient enough to activate action potentials in the calf muscle resulting in ankle flexion. The Revitive IX is designed to be used at home with minimal involvement from healthcare professionals. It can be used for up to 3 hours daily in 30 minute sessions. The retail cost of the device is approximately £160.

Although some evidence of the efficacy of NMES in the management of patients with IC exists, there is a significant paucity of high quality research conducted in a powered and controlled manner. The NESIC trial is vital to robustly identify the contribution of such devices compared to the current gold standard recommended practice of SET and the available standard of care offered in the majority of the UK and Ireland, which is BMT (including exercise advice).

## **Methodology**

The coordinating centre received research ethics committee approval (reference 17/LO/1918) and a letter of no objection from the UK Competent Authority. NESIC is registered on a public trials registry, ISRCTN: 18242823.

Figure 1 shows a consort diagram of the patient pathway through the study, and Table 1 details the inclusion and exclusion criteria. The study population comprises adults presenting to vascular outpatient clinics diagnosed with IC in one or both legs who meet all the inclusion exclusion criteria. NESIC is a two arm randomised controlled trial, where the control is best locally available therapy, which includes BMT AND either exercise advice or SET, depending on the centre. The intervention, in addition to the locally available therapy, is NMES.

### Centres where supervised exercise therapy is available

Following consent and administration of baseline assessments, patients will be randomised to BMT, SET *and* NMES, or BMT and SET only. Patients will be referred for SET classes as per local standard care. Compliance will be recorded via medical records as well as patient recorded diaries. Patients randomised to receive the NMES device will be trained how to use the equipment at home and advised to complete at least one pre-programmed 30 minute session of NMES per day. In line with the instructions for use, the device should be used for a minimum of 30 minutes per day up to a maximum of 3 hours per day. Patients will record compliance in a self-completed diary which will be cross referenced with a voltage/current data logger attached to a proportion of NMES devices.

### Centres where supervised exercise therapy is not available

Centres that do not provide SET will randomise patients to BMT (including exercise advice) *and* NMES, or BMT (including exercise advice) alone. Baseline assessments will be recorded in the same way as SET centres, and compliance to locally available BMT will be measured via drug compliance and smoking cessation at follow up visits.

The treatment phase of the study will be three months in duration and text message services will remind patients to either attend their SET classes and/or record in their diaries any unsupervised exercise they have performed, as well as to use and record usage of their NMES device (if in an NMES study arm).

Follow up for both centre types will be performed in the same way. The first follow up at 3 months, the end of the treatment period, will assess AWD using treadmill testing.

Haemodynamic assessments will be performed via laser Doppler flowmetry and duplex ultrasound to further understanding of underlying mechanisms. QoL questionnaires will be

performed as per the baseline assessment, and safety information will be recorded and reported to the UK Competent Authority in line with requirements.

The treadmill test, clinical examination, medication review, QoL questionnaires, laser Doppler flowmetry and safety reporting will occur at 6 months and again at 12 months follow up. Full details of the study assessments can be found in the study protocol, written in accordance with SPIRIT guidelines (18). The 12-month assessment marks the end of study participation, at which point patients will revert to standard care.

### Primary outcome

The primary endpoint of the study is AWD at 3 months as determined by a standardised treadmill test using the Gardner Skinner graded protocol (19). In this protocol, the treadmill starts at 3.2 km/h at a 0% incline, and the gradient of the treadmill is increased by 2% every 2 minutes. Patients indicate the start of their claudication pain, recorded as the initial claudication distance, and the test stops at the point the patient does not want to continue due to lower limb pain; this is the AWD. The patient will not be given a final score to prevent bias.

The 3-month intervention period is in line with NICE guidelines for SET. Four previous studies have reported on improvement in AWD for the same population of patients (20-23) with three of the studies reporting AWD at 3 months. These reported an improvement in AWD of between 75-90m (21-23). The improvement detected at 6 months varied from 41m (20) to 170m (21) across all studies. The MIMIC trial reported an improvement in AWD at 24 months but did not report the effect size at 3 months. None of the studies clearly reported the standard deviation associated with the treatment effect measurement. The MIMIC trial

assumed a standard deviation (SD) of 120m for an effect size of 60m in their sample size calculation.

### Secondary outcomes

Secondary outcomes, including resource use, adverse events, validated health related QoL questionnaires (EQ-5D-5L and SF36), and compliance data, will assist in modelling for economic evaluation of the intervention compared to standard treatment practice in order to assess cost effectiveness.

In addition to an assessment of clinical efficacy of NMES, haemodynamic measurements at the common femoral artery, including time averaged mean volume (TAMV, cm/s) and blood flow (cc/min) will be carried out by duplex ultrasound. In addition, skin microcirculation (blood flux) will be measured by laser Doppler flowmetry. These parameters will help further the understanding of underlying mechanisms for any changes in clinical and subjective outcomes.

### Sample size

From pilot work and clinical judgement, using NMES together with best locally available therapy should result in an improvement in mean AWD of at least 60m after 3 months in the intervention group. This improvement is deemed as clinically important. Therefore, we have adopted the same assumptions of effect size and standard deviation for the sample size calculation. These parameters are deemed as providing significant clinical benefit in the IC population, translating to an improvement in lifestyle factors as measured by QoL questionnaires.

The study has 90% power with a two sided  $\alpha = 0.05$  to detect a difference of 60m in the mean AWD at 3 months between the intervention and the control groups.

Assuming a 10% dropout rate, the sample size required for this study is 192 participants. The sample size was computed for a two sample means test using Stata (version 13, StataCorp).

### Study management and monitoring

In line with NIHR recommendations, a Trial Steering Committee (TSC) and independent Data Monitoring Committee (iDMC) have been appointed. An iDMC meeting will be held prior to first patient first visit, following completion of an internal pilot study, and will then be held one month prior to each TSC meeting. Full details of the iDMC's remit (including the stopping rules for effectiveness and futility) will be agreed in accordance with the charter at the first meeting, before any unblinded data are available or seen.

A Clinical Trial Manager together with the Trial Management Group will oversee trial progress.

### Data analysis

All randomised patients will be followed up to 12 months unless they specifically ask to be withdrawn, as per the intention to treat principle. In line with this type of analysis, patients lost to follow up or withdrawn from the study will not be replaced.

The primary analysis will estimate the difference between the groups in change from baseline AWD using an ANCOVA model with baseline AWD as a covariate. Repeated measure analysis, adjusted for stratification by centre, will investigate the relationship between AWD and one or more independent variables. Causal inference methods will be used to estimate

treatment effects that account for compliance with the allocated intervention (NMES, SET, BMT). Where necessary, data will be transformed to meet normality assumptions. The primary economic analysis will calculate costs and quality-adjusted life years (QALYs) over the duration of the trial and measured from EQ-5D-5L data collected in the trial. The decision model will use information from the trial and other sources to project costs and QALYs over the lifetime of the patients, by estimating the effect of IC on mortality, QoL and resource use, and the impact of the intervention on these endpoints.

All statistical tests will be two tailed with a 5% significance level. To recruit sufficient subjects, eight centres will participate in the study; four centres with exercise advice only as locally available therapy, and four providing SET.

### **Recruitment**

Once eligibility has been confirmed, subjects will be randomised to one of the two arms of the study and assigned a pseudonymised study number unique to each individual enrolled on the trial. Randomisation will be blocked with random block sizes and stratified by centre type.

Through feasibility data collected from each centre, a conservative estimate of 15 months is required to reach the target recruitment of 192 patients for this study, with each site aiming to recruit 24 patients in total.

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### **Conflicts of interest**

There are no conflicts of interest on the part of the authors.

Actegy Healthy Ltd, manufacturers of neuromuscular electrical stimulation devices supply Revitive IX devices to participants enrolled in NESIC.



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